PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32759A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/12594	International filing date *(day/month/year)* 11.11.2003	Priority date *(day/month/year)* 12.11.2002
International Patent Classification (IPC) or both national classification and IPC C07D487/04		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.05.2004	12.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Papathoma, S Telephone No. +49 89 2399-7536

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/12594

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-48 as originally filed

Claims, Numbers

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The application refers to 4-amino-5-phenyl-7-cyclohexyl-pyrrolo[2,3-d]pyrimidine derivatives suitable for the treatment of proliferative diseases.

Reference is made to the following documents:

D2: US-A-5 869 485 (MISSBACH MARTIN) 9 February 1999 (1999-02-09)
D3: US-A-6 051 577 (ALTMANN EVA) 18 April 2000 (2000-04-18)
D4: WO 97 28161 A (CIBA GEIGY AG ;ALTMANN EVA (CH); WIDLER LEO (CH); MISSBACH MARTIN) 7 August 1997 (1997-08-07) cited in the application
D5: WO 00 17203 A (BASF AG ;HIRST GAVIN C (US); RITTER KURT (US); ARNOLD LEE D (US);) 30 March 2000 (2000-03-30)
D6: WO 01 19829 A (BASF AG ;HIRST GAVIN C (US); RAFFERTY PAUL (US); RITTER KURT (US);) 22 March 2001 (2001-03-22)

1) Article 33(2) PCT

4-Amino-pyrrolo[2,3-d]pyrimidine derivatives having a cyclohexyl ring at their 7-position **and** a m-(-X-R^4) substituted phenyl ring at their 5-position are not disclosed in any of the available prior art documents. The subject matter of the present application is acknowledged thus to be novel according to Article 33(2) PCT.

2) Article 33(3) PCT

The problem outlined in the present application is to provide compounds, which are useful in the treatment of proliferative diseases. As the prior art (documents a) D2 column 4, lines 50-52, b) D3 column 5, lines 50-52, c) D4 page 8, lines 9-11 d) D5 page 10, line 11-page 14, line 5 and e) D6 page 44, lines 21-24 , page 61, lines 7-11 etc.) has already dealt with this problem, the actual technical problem may be seen in the provision of **further** compounds capable of treating proliferative diseases.

Alternative solutions to a known technical problem can be considered as inventive when it can be shown that they do not derive from the prior art in an obvious manner and that they indeed solve the problem eventually showing an unexpected effect.

With respect to the question whether the subject matter of the present application provides a "real" solution to the technical problem mentioned above, the biological tests provided in page 47 show that the disclosed examples do have the claimed activity.

With respect to the information given from the prior art and the question whether the solution provided by the present application can be derived in an obvious manner, the IPEA considers the claimed compounds as structurally close related to the entities disclosed in the prior art, and that the minor modification, which distinguishes them from the latter can be regarded as part of the synthetic routine of the person skilled in the art when looking for alternative solutions:

a) documents D2-D4 disclose the **benzyloxyphenyl substitution** and in particular D2 and D3 the m-benzyloxyphenyl substitution at the 5-position of pyrrolo[2,3-d]pyrimidine derivatives. The 7-position is substituted in case of D2, with a six- membered -but aromatic- carbocyclic ring, while in case of D3 with a five- or six- membered non aromatic ring, which, however, contains a nitrogen atom. In D4 a cyclopentyl substitution is disclosed at the 7-position of the pyrrolo[2,3-d]pyrimidine derivatives and a p-benzyloxyphenyl at the 5-position.

b) document D5, on the other hand discloses pyrrolo[2,3-d]pyrimidine derivatives substituted by a **cyclohexyl ring** at the 7-position, and by a p-phenoxyphenyl or a p-(cyclic ring-(sulphon)amido)- phenyl group at the 5-position.

c) document D6, although referring to pyrrazolopyrimidine derivatives, discloses in the examples 329 and 332-334 the **combination of the cyclohexyl with an heteroaryl-methylamino-phenyl substitution.**

Since, apart of document D5 there is a plurality of prior art disclosing 4-amino-7-cyclohexyl-pyrrolo[2,3-d]pyrimidine derivatives, the introduction of a m-benzyloxyphenyl or an heteroaryl-methylamino-phenyl substitution as disclosed in documents D2-D4 and D6 respectively can be considered to belong in the synthetic routine of a person skilled in the art when looking for alternative solutions to a known and solved chemical problem. Therefore on the basis of the information given by the documents D2-D6 the subject matter of the present application is considered as an obvious selection of D4/D5 and as not to involve inventive ingenuity, and thus does not fulfill the requirements of Article 33(2) PCT.

Regarding the possibility of the presence of inventive merit for a "selection invention", it must be mentioned that an inventive merit can only be acknowledged in the case that the claimed subject matter shows unexpected effects with respect to the closest prior art. Consequently, for a possible reconsideration regarding the evaluation of the inventive merit of the subject matter of the present application, further evidence will be needed, where the properties of the claimed compounds are compared with those of the structural more related compounds.

3) Furthermore, the sole exemplification of the -X-R^4 moiety being a benzyloxy group in the

disclosed examples does not justify the breadth of claims **(Article 6 PCT: fully supported by the description).**

The applicant is entitled to claim only obvious modifications of what was described (close related variations), since the claims should represent a reasonable generalisation of the examples given in the description: the technical features stated in the description/examples as being essential features of the invention described must be the same as those used to define the invention in the claims. The reason for that is that the problem to be solved **should be solved by the whole scope of the claimed subject matter** (every compound falling within its scope) and not just by individual compounds. If this were not the case, an invention could arbitrarily be broadened to any limit without consideration, whether the compounds are actually solving the problem underlying the invention.

4) Document:

D1: WO 02 092599 A (NOVARTIS ERFIND VERWALT GMBH ;MANLEY PAUL WILLIAM (CH); NOVARTIS A) 21 November 2002 (2002-11-21)

can not be considered as prior art document according to the Article 33(2) PCT, because it is published after the priority day and before the filing day of the application. However care should be taken by the applicant while entering the regional phase, because this document could be relevant for the examination, as it refers to close structurally related 4-amino-pyrrolo[2,3-d]pyrimidine derivatives, which differ from the claimed entities in the presence of a cyclobutyl ring in the place of the present cyclohexyl ring.